GMPC-Thesis and Opinions Platform

eISSN:2747-5735

Review

Can Lufenuron be an alternative treatment option in small animal dermatomycosis?

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Article History:
Received: 24-Nov-2021
Accepted: 10-Dec-2021
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Abstract

Lufenuron (Benzoyl-phenyl urea) is a chitin synthesis inhibitor that inhibits chitin production. It has an ectoparasitic effect by causing impairment in chitin biosynthesis and larval development of various parasite species. Lufenuron is an agent that is effectively used as a pesticide against agricultural pests in the ecosystem and veterinary medicine. It is used to control various ectoparasites such as fleas and scabies of cats and dogs. The high prevalence of mycotic diseases in pet animals, especially in cats and dogs, and the increasing drug resistance in veterinary medicine reveal the importance of different treatment options. The purpose of this review is to evaluate the effectiveness of the lufenuron as a new antimycotic agent in veterinary medicine.

Keywords: Lufenuron, Antimycotic, Veterinary medicine, Dermatomycosis

Citation: Bilgiç, B., Dokuzeylül, B., Bakay, B. B. and Or, M. E. 2021. Can Lufenuron be an alternative treatment option in small animaldermatomycosis. GMPC TOP (2): 15-18.
https://doi.org/10.51585/gtop.2021.2.0009

Introduction

Lufenuron (Benzoyl-phenyl urea) is a chitin synthesis inhibitor that blocks chitin production of various insect species (Wilson and Cryan, 1997). Chitin is a primary component of fungi cell walls, the exoskeletons of arthropods, and a structural component in protozoa and nematodes (Mansur et al., 2010). Lufenuron suppresses the developmental stages in the life cycle of insects by causing disruptions in chitin biosynthesis and cuticular lesions during larval development (Bogwitz et al., 2005; Adel, 2012). Because of its low potential toxic effects on vertebrates and low environmental pollution potency, it has been considered a pesticide in agricultural activities (Farrag and Shalby, 2007) against leafworms in the ecosystem (Piri Aliabadi et al., 2016); cockroaches and fleas in home environments (Mosson et al., 1995).

In addition, lufenuron plays an important role in combating corn and vegetable pests such as *Lepidoptera* and *Coleoptera* (Farrag and Shalby, 2007; Sáenz-de Cabezón et al., 2006; do Nascimento et al., 2015). Furthermore, Lufenuron has shown high effectiveness in the control of citrus rust mite *Phyllocoptruta oleivora* (Bueno and Freitas, 2004), *Helicoverpa armiger*, and *Pectinophora gossypiella* (Butter et al., 2003; Kandil et al., 2012), which cause significant damages in cotton production in countries such as India and Egypt.

In addition to its use in agriculture, its therapeutic effect in mammals has also been proved. Since there is no chitin in mammalian cells, lufenuron can be used as an ectoparasitic compound in animals without causing any toxic effects on the host (DeBoer et al., 2003). Despite being safe in mammals, a recent study showed the lufenuron reproductive toxicity and genotoxic effects in pregnant albino rats (Basal et al., 2020).

The cat flea *Ctenocephalides felis*, one of the most common ectoparasites of cats and dogs, has been very successfully treated with the oral use of lufenuron and has taken its place in the market as tablet form (Shipstone and Mason, 1995; Dean et al., 1998; Dryden et al., 2012; Rust, 2005, 2020). Although the main area of its use in veterinary medicine is for flea infestations prophylaxis, and therapeutic purposes, it has been thought that lufenuron can be an effective treatment for mycotic diseases in animals (Guillot et al.,

2002). In addition, the prevalence of mycotic diseases and the increasing drug resistance cause different treatment options to be considered. This review aims to evaluate the use of lufenuron active ingredient as an antimycotic treatment option in veterinary medicine.

Pesticidal effect of lufenuron

Lufenuron shows its effect on the chitin layer, which constitutes approximately 25-50% of the parasite's body weight. After oral administration, due to its high lipophilic properties, it accumulates in adipose tissue and gradually enters the bloodstream. Lufenuron passes into the female flea by the bites of its host and joins the structure of the flea eggs. It causes deterioration in larval development periods and larval death (Shipstone and Mason, 1995). A study investigating its effect on fleas showed that lufenuron resulted in a decrease in flea burden up to 97% within 70 days when administered for 7 days after infestation (Smith et al., 1996).

Another study found an ovicidal effect of up to 100% in dogs treated with an injectable combination of milbemycin oxime and lufenuron (Novartis®) (Dryden et al., 2012). In a study evaluating the efficacy of a single dose administered subcutaneously, lufenuron has been reported to be more than 90% effective up to 26 weeks in treating *Ctenocephalides felis* infestation in cats (Franc and Cadiergues, 1997). In contrast, lufenuron was found ineffective in controlling generalized demodicosis (demodectic mange) in dogs despite high drug levels being measured in the skin of affected animals (Schwassmann et al., 1997).

Antimycotic activity of lufenuron

Few studies have also been conducted to investigate the antimycotic activity of lufenuron. The wall of fungal cells consists of polysaccharides, chitosan, glucan, mannan, and primarily chitin (Ben-Ziony and Arzi, 2000). Similar to ectoparasites, chitin is a primary component of fungal cell walls. Based on the studies conducted on chemicals that inhibit chitin and β-1,3-glucan synthesis in the fungal cell wall (Palli and Retnakaran, 1999; Urbina et al., 2000), it was thought that compounds such as lufenuron might also have antifungal effects (DeBoer et al., 2003). However, in a study conducted to evaluate the effectiveness of lufenuron against *Coccidioides immitis*, no inhibitory effect of lufenuron *in-vitro* or *in-vivo* (in mice) using oral and injectable formulations has been found (Johnson et al., 2008).

In another similar study, the effectiveness of lufenuron on *Coccidioides immitis* and *Aspergillus fumigatus* was examined *in-vtro*, and it was emphasized that this compound was not effective on both mycosis (Hector et al., 2005). *Candida* spp. and *Aspergillus* spp. are the most common fungal endometritis agents in mares. In a study evaluating lufenuron effectiveness as uterine lavage in mares diagnosed with fungal endometritis, the culture made on the 5th day after the application showed no aerobic bacteria or fungal growth. However, in the same study, it was observed that *Candida paratropicalis* recurred intensively in culture media performed 5 weeks after the drug administration (Hess et al., 2002).

On the other hand, lufenuron showed no effect on the *in-vitro* growth of *Aspergillus* or *Fusarium* spp. isolated from the cornea of horses diagnosed with keratomycosis (Scotty et al., 2005). These data indicated that using lufenuron as an antifungal agent is probably strains specific that need further investigation.

Lufenuron as an alternative treatment for dermatomycosis

In a study investigating the effect of lufenuron on dermatophytosis, the dosages of 51.2-266 mg/kg and 53.2-102.3 mg/kg were administered to dogs and cats diagnosed with dermatophytosis, respectively. The hair growth was observed by the 10-11th days in dogs and the 5-6th days in cats. Complete recovery occurred within 16-21 days in dogs and 10-12 days in cats. In dogs diagnosed with dermatomycosis (*A. niger*, *A. terreus*, *C. albicans*), lesions improvement was recorded 17-34 days after lufenuron treatment with no adverse effects (Ben-Ziony and Arzi, 2000).

In contrast, another study showed no *in-vitro* effect of lufenuron on dermatophytes isolated from dogs and cats. Additionally, the *in-vivo* administration of two doses (70-100 mg/kg) every two weeks in cats and dogs failed to treat dermatophytosis; however, the immunomodulatory effect of the drug was suggested due to the improvement of non-dermatophytes lesions (Zur and Elad, 2006). The protective effect of lufenuron against the spores in healthy cats in contact with *Microsporum canis* infected animals was investigated. It was observed that the use of lufenuron in healthy cats was not effective in the prophylaxis of dermatophytosis (Moriello et al., 2004). In another similar study, oral or subcutaneous administration of lufenuron did not prevent contamination with *Microsporum canis* infected cats, and clinical improvements in affected cats occurred in a similar period as in the control group (DeBoer et al., 2003).

In cases where lufenuron is used alone, although sufficient antimycotic effect and clinical improvement can not be achieved, mild inhibition may occur. For this reason, to evaluate the possible synergism when used with a different antimycotic agent, various drug combinations were formulated and evaluated. However, drugs such as terbinafine and itraconazole were combined with various drugs, including lufenuron, did not reveal a significant synergism (DeBoer et al., 2004).

Conclusions

Since lufenuron is a chitin biosynthesis inhibitor, it was suggested as an effective agent in dermatophytosis treatment. Although there is an urgent need for new antimycotic treatment options in veterinary medicine; however, based on the studies conducted, we believe that a sufficient antimycotic effect cannot be obtained with lufenuron in mycotic infection in animals. Eventually, our opinion is more studies are needed to investigate the synergistic effects of lufenuron and other substances.

Article Information

Funding. This research received no external funding.

Conflict of Interest. The authors declare no conflict of interest.

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